Claims 1-11 are pending in the present application. Claims 3-10 are canceled herein without prejudice. Claims 1-2 are amended herein. Support for these claim amendments can be found in the claims as filed and throughout the specification. New claims 12-17 are added herein. Support for new claims 12 and 13 can be found in the claims as filed and on page 41, line 3 of the specification. Support for new claims 14 and 16 can be found in the claims as filed and on page 41, line 27 of the specification. Support for new claims 15 and 17 can be found in the claims as filed and on page 41, line 2, page 42, lines 22-23 and page 53, lines 22-23 of the specification. It is believed that no new matter has been added by these amendments. In light of these amendments and the following remarks, applicants respectfully request entry of the new claims, reconsideration of the application and allowance of the pending claims to issue.

I. Objection to the Oath/Declaration

The Office Action states that the oath or declaration is defective because non-initialed and/or non-dated alterations have been made to the oath or declaration.

Attached hereto is a Petition to Correct Inventorship Pursuant to 37 C.F.R. § 1.48(a) where applicants request that Dr. Brian Safer be deleted as a co-inventor. The inventorship originally set forth in the application was in error in naming Dr. Safer, without deceptive intent on the part of the named inventors, or on the part of any other party or parties. The inventors of the present invention are John A. Chiorini, Robert M. Kotin, Beverly Davidson and Joseph Zabner. Therefore, attached hereto, accompanying the Petition to Correct Inventorship, is a Declaration executed by the actual inventors pursuant to 37 C.F.R. § 1.63. While there are hand-written alterations to the addresses of

some of the inventors, these alterations are initialed and dated by the maker of the alterations. Thus, there should be no objection on this ground.

II. Rejection Under 35 U.S.C. § 112, first paragraph

The Office Action states that claims 1-11 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for the claimed method of delivering a nucleic acid, wherein intranasal administration of AAV5 particles is used to deliver the nucleic acid to an alveolar cell and direct injection into the brain is used to deliver a nucleic acid to a cerebellar cell or an ependymal cell, the specification allegedly does not reasonably provide enablement for the claimed methods, wherein another mode of administration is employed.

Claims 3-10 are cancelled herein. Claim 1 is amended herein to recite, in relevant part, "a method of delivering a nucleic acid to an alveolar cell, *in vitro*." Claim 2 is amended herein to recite, "a method of delivering a nucleic acid to an alveolar cell in a subject comprising administering to the subject an AAV5 particle comprising the nucleic acid inserted between a pair of AAV inverted terminal repeats, wherein the nucleic acid is delivered intranasally, thereby delivering the nucleic acid to an alveolar cell in the subject." New claim 12 recites a "method of delivering a nucleic acid to an alveolar cell in a subject comprising administering to the subject an AAV5 particle comprising the nucleic acid inserted between a pair of AAV inverted terminal repeats, wherein the nucleic acid is delivered via aerosol, thereby delivering the nucleic acid to an alveolar cell in the subject." New claim 13 recites a "method of delivering a nucleic acid to an

alveolar cell in a subject comprising administering to the subject an AAV5 particle comprising the nucleic acid inserted between a pair of AAV inverted terminal repeats, wherein the nucleic acid is delivered via the airway, thereby delivering the nucleic acid to an alveolar cell in the subject." New claim 14 recites, in relevant part, "a method of delivering a nucleic acid to a cerebellar cell, *in vitro*." New claim 15 recites a "method of delivering a nucleic acid to a cerebellar cell in a subject comprising administering to the subject an AAV5 particle comprising the nucleic acid inserted between a pair of AAV inverted terminal repeats, wherein the AAV5 particle is delivered directly to the brain of the subject, thereby delivering the nucleic acid to a cerebellar cell in the subject." New claim 16 recites, in relevant part, "a method of delivering a nucleic acid to an ependymal cell, in vitro." New claim 17 recites a "method of delivering a nucleic acid to an ependymal cell in a subject comprising administering to the subject an AAV5 particle comprising the nucleic acid inserted between a pair of AAV inverted terminal repeats, wherein the AAV5 particle is delivered directly to the brain of the subject, thereby delivering the nucleic acid to an ependymal cell in the subject."

Since amended claim 1, new claim 14 and new claim 16 are directed to *in vitro* methods of delivering a nucleic acid to an alveolar cell, a cerebellar cell and an ependymal cell, respectively, the problems cited by the Examiner regarding *in vivo* targeting of cells does not apply to these claims.

Amended claim 2, new claim 12 and new claim 13 are directed to methods of delivering a nucleic acid to an alveolar cell in a subject intranasally, via aerosol and via the airway, respectively. The Examiner has stated that applicants have enabled the claimed method of delivering a nucleic acid, wherein intranasal administration of AAV5

particles is used to deliver the nucleic acid to alveolar cells. Thus, amended claim 2 is enabled. New claim 12 is directed to a method of delivering a nucleic acid via aerosol delivery, which is described in the specification on page 41, line 3. Therefore, applicants believe that one of skill in the art would read the specification and recognize that aerosol delivery would be expected to be effective in delivering the vector to the alveoli for the same reason that intranasal delivery is effective, i.e., both route via the airway. Thus, applicants believe that new claim 12 is also enabled. New claim 13 is directed to delivery of the nucleic acid to an alveolar cell via the airway. One of skill in this art would recognize that a nucleic acid to be delivered to an alveolar cell in the lungs could routinely and with certainty be delivered via the airway (nose, mouth, trachea, bronchii, bronchioles, etc.). The mechanism of such delivery is exemplified by intranasal delivery. Because intranasal delivery is via the airway, there is no scientific basis to assert that the other well-recognized means of delivery via the airway would not be within the routine skill of one of skill in this art.

With regard to new claims 15 and 17, these claims are directed to delivery of a nucleic acid to a cerebellar cell and an ependymal cell, respectively, via direct delivery to the brain. The Examiner has stated that the application is enabled for the deliver of a nucleic acid to a cerebellar cell or an ependymal cell, via injection. Furthermore, there are several well-recognized and routine methods for direct delivery of substances to the brain, for example, intrathecal, intracisternal , intraventricular or trans-sphenoidal delivery via catheter or needle (See attached abstracts of Kelly et al., Bassiouny et al., Chamberlain and Lange et al., showing the use of these methods in the art). Because of the existence of these methods at the time the present application was filed, methods of

delivering the vector of the invention to the brain via these methods, as in claims 15 and 17, are enabled. Thus, applicants believe that this rejection has been overcome and respectfully request its withdrawal.

III. Rejection Under 35 U.S.C. § 112, second paragraph

The Office Action states that claim 7 is rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 7 is canceled herein, thus rendering this rejection moot. Therefore, applicants respectfully request withdrawal of this rejection.

IV. Rejections Under 35 U.S.C. § 102(e)

A. Office Action states that claims 1-3, 6, 7, 10 and 11 are rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 6,309,634 (Bankiewicz et al.). According to the Office Action, the claims are directed to a method of delivering a nucleic acid to a cell by administering an AAV5 particle containing a nucleic acid inserted between a pair of AAV inverted terminal repeats. Claims 2, 7 and 10 are specifically directed to delivering a pair of AAV inverted terminal repeats. The Office Action further states that Bankiewicz et al. discloses a method for treating Parkinson's disease in a subject by administering recombinant AAV virions to brain cells. The specification explicitly states that AAV5 vector may be used in the invention. Furthermore, the specification explicitly states that the AAV ITR may be derived from

AAV5. Thus, the Office Action concludes that the claimed method is disclosed in the prior art.

As stated above, claims 3, 6, 7 and 10 are canceled herein. Claims 1 and 2 are amended herein to recite, in relevant part, "a method of delivering a nucleic acid to an alveolar cell." New claims 12 and 13 are also directed to a method of delivering a nucleic acid to an alveolar cell. New claims 14-15 are directed to methods of delivering a nucleic acid to a cerebellar cell. Also, new claims 16-17 are directed to methods of delivering a nucleic acid to an ependymal cell. U.S. Patent No. 6,309,634 (Bankiewicz et al.), does not disclose or suggest the delivery of a nucleic acid to an alveolar cell, a cerebellar cell or an ependymal cell. Therefore, U.S. Patent No. 6,309,634 (Bankiewicz et al.) does not anticipate claims 1-2, new claims 12-17 or claim 11 which depends from any of claims 1-2 and 12-17. Thus, applicants believe this rejection has been overcome and respectfully request its withdrawal.

B. The Office Action states that claims 1 and 2 are rejected under 35 U.S.C. 102(e) as allegedly being anticipated by U.S. Patent No. 6,391,858 (Podsakoff et al.)

Applicants respectfully point out to the Examiner that the filing date of U.S. Patent No. 6,391,858 is January 4, 2001. The present application was filed on March 22, 2000. Therefore, applicants believe that U.S. Patent No 6,391,858 is improperly cited and should not be a prior art reference against the present application. Thus, applicants respectfully request the withdrawal of this rejection.

C. Claims 1 and 2 are rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 6,221,349 (Couto et al.). According to the Office Action,

Couto et al. discloses a method of delivering a nucleotide sequence to a mammal by administering a recombinant AAV virion to the mammal. The specification explicitly states that AAV5 vectors may be used in the invention. Furthermore, the specification explicitly states that the AAV ITR may be derived from AAV5.

Claims 1 and 2 are amended herein to recite, in relevant part, "a method of delivering a nucleic acid to an alveolar cell." New claims 12 and 13 are also directed to a method of delivering a nucleic acid to an alveolar cell. New claims 14-15 are directed to methods of delivering a nucleic acid to a cerebellar cell. Also, new claims 16-17 are directed to methods of delivering a nucleic acid to an ependymal cell. U.S. Patent No. 6,221,349 (Couto et al.), does not disclose or suggest the delivery of a nucleic acid to an alveolar cell, a cerebellar cell or an ependymal cell. Therefore, U.S. Patent No. 6,221,349 (Couto et al.) does not anticipate claims 1-2, new claims 12-17 or claim 11 which depends from any of claims 1-2 and 12-17. Thus, applicants believe this rejection has been overcome and respectfully request its withdrawal.

V. Rejection Under 35 U.S.C. § 103(a)

The Office Action states that claims 1-3, 6, 7, 10 and 11 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Patent No. 6,180,613 (Kaplitt et al.) and Georg-Fries et al. According to the Office Action, Kaplitt et al. disclose a method for ameliorating a symptom of a central nervous system disorder in a mammal by administering an AAV vector to a target cell in the brain of the mammal. The Office Action further states that claim 11 specifically recites that the target cell is in the cerebellum and that the specification and claims read broadly on AAV vectors of any

subtype, including AAV5. Also stated in the Office Action is that Georg-Fries et al. discloses that type 5 adeno-associated virus has been known in the art since 1984. Further stated in the Office Action is that since AAV5 has been known in the art since 1984 and since the claims of Kaplitt et al. read broadly on AAV vectors of any subtype, it is evident that in 1995 Kaplitt contemplated using AAV vectors, as well as AAV vectors of other subtypes, in practicing the claimed methods. Therefore, the Office Action concludes that the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

As stated above, claims 3, 6, 7 and 10 are canceled herein. Claims 1 and 2 are amended herein to recite, in relevant part, "a method of delivering a nucleic acid to an alveolar cell." New claims 12 and 13 are also directed to a method of delivering a nucleic acid to an alveolar cell. New claims 14-15 are directed to methods of delivering a nucleic acid to a cerebellar cell. Also, new claims 16-17 are directed to methods of delivering a nucleic acid to an ependymal cell.

Applicants respectfully point out to the Examiner that merely disclosing the existence of AAV5 in Georg-Fries et al. did not provide a basis for expecting that AAV5 could be used as a vector to deliver nucleic acids to the specific cell types (e.g. alveolar cells, cerebellar cells and ependymal cells) described and claimed by applicants in the present application. In fact, Georg-Fries et al. provides no AAV5 sequences, thus providing no chemical structure for any AAV5 sequence. Thus, it was not until the present applicants disclosed how to utilize the AAV5 genome and its subsequences as vectors to deliver nucleic acids to alveolar cells, cerebellar cells and ependymal cells, that one could have known that AAV5 had properties that would make it useful as a vector for

delivery to these specific cell types. Furthermore, although the Office Action states that the specification and claims of Kaplitt et al. read broadly on AAV vectors of any subtype, including AAV5, Kaplitt et al. provides no AAV5 sequences nor any guidance as to how to utilize the AAV5 genome and its subsequences for delivery of nucleic acids to any cell, much less to alveolar cells, cerebellar cells and ependymal cells. The teachings of Kaplitt et al., like the teachings of Georg-Fries, are insufficient to allow one of skill in the art to utilize the AAV5 genome and its subsequences as a vector for delivery of a nucleic acid to a cell. Therefore, even if the skilled artisan should contemplate utilizing AAV5 as a vector based on the teachings of Georg-Fries et al. and Kaplitt et al., both references are inadequate to provide what is necessary to have a reasonable expectation of success. Thus, one of skill in the art could not have combined the teachings of Kaplitt et al. with those of Georg-Fries et al. to arrive at the claimed invention. Therefore, applicants believe this rejection, as it pertains to amended claims 1-2 and new claims 12-17 has been overcome. Thus, applicants respectfully request its withdrawal.

Pursuant to the above amendments and remarks, reconsideration and allowance of the pending application is believed to be warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

A Credit Card Payment Form PTO-2038 authorizing payment in the amount of $930.00 (three (3) month extension of time fee) is enclosed. This amount is believed to

be correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

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CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents, P.O. Box 1450, Alexandra, VA 22313-1450, on the date shown below.

Gwendolyn D. Spratt — Date: 4-4-03

Marked-Up Version of Claim Amendment
U.S. Serial No. 09/533,427

1. (Amended) A method of delivering a nucleic acid to an alveolar cell, *in vitro*, comprising administering to the alveolar cell an AAV5 particle containing a vector comprising the nucleic acid inserted between a pair of AAV inverted terminal repeats, thereby delivering the nucleic acid to the cell.

2. (Amended) A method of delivering a nucleic acid to an alveolar cell in a subject comprising administering to the subject an AAV5 particle comprising the nucleic acid inserted between a pair of AAV inverted terminal repeats, wherein the nucleic acid is delivered intranasally, thereby delivering the nucleic acid to an alveolar cell in the subject.

11. (Amended) The method of any of claims [1-10] 1-2 and 12-17, wherein the AAV inverted terminal repeats are AAV5 terminal repeats.